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Citation

Crispín, José C., and George C. Tsokos. 2010. IL-17 in systemic lupus erythematosus. *Journal of Biomedicine and Biotechnology* 2010: 943254.

Published Version

doi:10.1155/2010/943254

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Review Article

IL-17 in Systemic Lupus Erythematosus

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Received 5 February 2010; Accepted 7 February 2010

Academic Editor: Brian Poole

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IL-17 is a cytokine with powerful proinflammatory activity. Production of IL-17 is abnormally increased in patients with systemic lupus erythematosus (SLE), a multiorgan chronic autoimmune disease. In patients with SLE, CD3⁺CD4[−]CD8[−] (double negative) T cells are an important source of IL-17. IL-17 produced by double negative and CD4 T cells participates in the pathogenesis of the disease. IL-17-producing T cells are present in the kidneys of patients with lupus nephritis. IL-17 increased production in patients with SLE can amplify the immune response by increasing target organ inflammation and damage and by augmenting the production of antibodies by B cells.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder that appears in genetically prone individuals triggered by ill-defined environmental factors [1]. Patients with SLE develop an immune response against numerous, mostly intracellular self-antigens. This chronic response alters the function of the immune system and releases self-antigens that along with autoantibodies form immune complexes that deposit in susceptible vascular beds, mostly in skin, joints, and renal glomeruli. Immune complex deposition causes local inflammation and tissue damage that probably amplify the autoimmune response creating thus a vicious cycle.

Cytokines are intimately involved in SLE pathogenesis. They contribute to the underlying immune dysfunction and to immune-mediated events that damage target organs. IL-17 is a cytokine with powerful inflammatory properties. Recent evidence suggests that it is involved in the pathogenesis of SLE. In this paper, we discuss the evidence that links IL-17 to SLE in both human and animal models. Data indicates that IL-17-driven inflammation amplifies SLE-induced tissue damage and contributes to tolerance breakdown in SLE patients.

2. Interleukin-17

Interleukin (IL)-17 is an ancient cytokine intimately related with epithelia—particularly with the intestinal mucosa [2, 3]. Its main receptor, IL-17RA, is broadly expressed on epithelial and endothelial cells as well as on immune cells [4–6]. It is produced by several cell types including activated T cell subsets (CD4⁺, CD8⁺, and TCR- $\alpha\beta$ CD4[−] CD8[−], TCR- $\gamma\delta$), natural killer cells, and neutrophils [7]. IL-17 plays an essential role in the immune response against bacteria and fungi [8].

IL-17 has pro-inflammatory capacities exerted through its ability to induce secretion of chemokines such as IL-8, monocyte chemoattractant protein-1 (MCP-1), and growth-related oncogene protein- α , which recruit monocytes and neutrophils [9–12]. IL-17 also facilitates T cell activation and infiltration into tissues by upregulating the expression of intercellular adhesion molecule-1 (ICAM-1) and amplifies the immune response by inducing the production of IL-6, prostaglandin E₂, granulocyte-macrophage colony stimulating factor (GM-CSF), and granulocyte colony stimulating factor [13–15]. Additionally, IL-17 acts synergistically with other cytokines, particularly IL-1 β , tumor necrosis factor (TNF)- α , and interferon (IFN)- γ [13, 16].

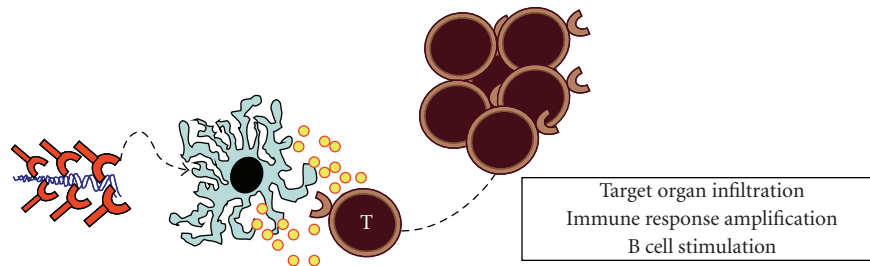


FIGURE 1: The IL-17 response is amplified in SLE. Nucleic acid-containing immune complexes and other inflammatory stimuli (e.g., cytokines) induce the production of pro-inflammatory cytokines by dendritic cells. These factors, along with others not yet identified, favor the generation of pro-inflammatory IL-17-producing T cell subsets (i.e., T_H17 and DN T cells) able to migrate to target organs and inflict damage. Produced IL-17 amplifies the inflammatory response and stimulates other cell types (e.g., B cells).

IL-17-producing cells have been recently implicated in the pathogenesis of a wide range of inflammatory and autoimmune diseases including psoriasis, rheumatoid arthritis (RA) [17, 18], inflammatory bowel disease (IBD) [19], systemic sclerosis [20], and systemic lupus erythematosus (SLE) [21, 22].

3. IL-17 Production in SLE

Evidence indicates that production of IL-17 is abnormally high in patients with SLE. Its levels are increased in SLE sera [23] and correlate with SLE disease activity [22, 24]. Moreover, the frequency of IL-17-producing T cells is increased in the peripheral blood of patients with SLE [21, 22, 25].

A significant fraction of the IL-17 produced in SLE patients derives from double negative (DN) $TCR-\alpha\beta^+CD4^-CD8^-$ T cells [21]. DN T cells represent a small T cell subset in healthy individuals. These cells are expanded in peripheral blood of SLE patients and produce pro-inflammatory chemokines and cytokines including IL-17, $IFN-\gamma$, and IL-1 β [26]. Support for their pathogenic role derives from the fact that IL-17-producing T cells have been observed in kidneys of patients with lupus nephritis [21, 27], among infiltrates rich in DN T cells [21].

Apart from its direct pro-inflammatory activity, the effects of IL-17 in other cell types may contribute to SLE pathogenesis. Increased production of total IgG, anti-dsDNA IgG, and IL-6 by peripheral blood mononuclear cells of patients with lupus nephritis was observed when they were cultured in the presence of IL-17 [28]. These findings suggest that IL-17 may participate in the activation of B cells in patients with SLE.

IL-17 production is also high in mice affected by lupus-like diseases [29]. An abnormally high fraction of T cells from MRL/lpr mice produce IL-17 [29]. In these mice, as in patients with SLE, DN T cells are an important source of IL-17. Interestingly, lymph node cells derived from MRL/lpr mice were able to cause glomerulonephritis when transferred into lymphocyte-deficient $Rag^{-/-}$ mice. The effect depended on their prestimulation with IL-23, a cytokine known to stimulate IL-17 production in humans and mice [29]. IL-17, along with IL-13 and $IFN-\gamma$, is the main cytokine produced

by infiltrating T cells in nephritic kidneys of MRL/lpr mice [29, 30].

In SNF1 mice (New Zealand Black x SWR F1), spleen cells produce significantly higher amounts of IL-17 than spleen cells from control mice when cultured in the presence of nucleosomes, a known lupus autoantigen [31]. In these mice as in the MRL/lpr, IL-17-producing T cells are detected in kidneys affected by nephritis. Interestingly, clinical disease improved along with decreased IL-17 production in mice treated with a tolerating regime induced with a histone-derived peptide [31], or with nasal administration of anti-CD3 [32].

The BXD2 mouse, a model that spontaneously develops arthritis, glomerulonephritis, and autoantibodies [33], has high IL-17 levels in serum as well as increased numbers of IL-17 $^+$ cells in the spleen [34]. Accordingly, upon stimulation an increased fraction of BXD2 T cells produce IL-17. Humoral responses are strongly augmented in these mice [35]. They spontaneously develop germinal centers (GC) in the spleen where IL-17 $^+$ T cells colocalize with IL-17R $^+$ B cells [34]. The importance of IL-17 in this process was demonstrated when B6 and predisease BXD2 mice were infected with an IL-17-coding adenovirus that increased IL-17 levels and induced the formation of germinal centers in both mouse strains. Concordantly, formation of GC diminished and production of anti-DNA and anti-histone antibodies was abrogated in BXD2 IL-17R deficient mice [34]. This supports the concept that IL-17 can provide help to B cells.

4. Amplification of the IL-17 Response in SLE

IL-17 is the prototypical cytokine of a CD4 T cell effector subset known as T_H17 cells [7]. T_H17 cells are generated when naïve CD4 T cells are primed in the presence of TGF- β and certain inflammatory cytokines (i.e., IL-21, IL-6, and IL-23) [36–38]. Patients with SLE have a higher frequency of IL-17-producing T cells [21, 22, 25]. It is thus assumed that the generation of T_H17 cells is favored in SLE patients. Nevertheless, this has not been directly addressed in any study. Moreover, cells different than CD4 T cells are important sources of IL-17 and particularly in SLE, DN T cells are important producers of this cytokine [21].

From a theoretical point of view, the SLE environment is ideal for the generation of T_H17 cells. T cells from patients with SLE produce abnormally low levels of IL-2 [39], a cytokine able to prevent the generation of T_H17 cells and favor that of regulatory T cells [40, 41]. Moreover, production of the inflammatory cytokines IL-6 and IL-21 is enhanced in cells derived from patients with SLE [42, 43]. Plasmacytoid dendritic cells can induce the conversion of CD4 T cells into T_H17 cells after stimulation through TLR7 [44]. In patients with SLE, who have circulating immune complexes that contain nucleic acids, this could represent an important mechanism for the amplification of the T_H17 response (Figure 1).

In summary, IL-17 production is increased in patients with SLE. Elevated IL-17 levels probably contribute to the recruitment and activation of immune cells (e.g., neutrophils and T cells) to target organs and thus amplify an ensuing immune response. The immune environment in patients with SLE is ideally suited for the generation of IL-17-producing T cells. Produced IL-17 probably has broad effects on the immune system that include B cell stimulation [24]. The precise pathways through which IL-17 contributes to SLE pathology will need to be identified in future work.

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